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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,397	10/02/2000	Lars Eric Sundstrom	MAR37P-314	9763

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	18

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/581,397	Applicant(s) SUNDSTROM ET AL.	
	Examiner David Lukton	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *3,4,7 and 9-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 6, 8, 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 17 (filed 4/21/03), claims 1, 19, 23, 24 have been amended.

Claims 3, 4, 7, 9-18 remain withdrawn from consideration. Claims 1, 2, 5, 6, 8, 19-24 are examined in this Office action.

Applicants' arguments filed 4/21/03 have been considered and found persuasive in part. The rejection of claims 1, 2, 5, 6, 8, 19-24 under 35 U.S.C. §112 second paragraph is withdrawn. However, the previously imposed §103 rejections are maintained.

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The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947).

As indicated previously, Cherksey teaches (cols 7-12) various compounds falling within the scope of the claimed genus, including (cols 9-10) compound "R".

There are fundamentally two issues here. First, is the disclosure of various compounds falling within the scope of the claimed genus sufficient to render the claimed genus obvious, and second, does Cherksey provide an adequate description and an enabling disclosure of how to synthesize the claimed compounds? The arguments in this response (filed 4/21/03) have focused exclusively on the second of these two questions.

The response filed 4/21/03 attributes to the examiner an assertion that Cherksey fails to teach or suggest that the claimed compounds are of the L-configuration. However, no such statement has been made by the examiner. What was stated by the examiner is that the reference does not disclose that the compounds "must" be of the L-configuration. While the reference may not disclose that the compounds "must" be of the L-configuration, the reference does provide both an explicit teaching of the L-configuration and an implicit teaching of the same. First, the convention among peptide chemists is for the stereochemistry of a given amino acid (or molecule containing an amino acid) to be of the L-configuration unless indicated otherwise. Thus, the ordinarily skilled peptide chemist would have regarded the chiral center (of the carbon bearing the alpha-amino group) of the

various compounds in columns 7-12 as being of the L-configuration, since there is no indication to the contrary. In addition, the L-isomer of arginine was used rather than the D-isomer, in the procedure to which applicants have referred (col 18, line 54+). Thus, the reference provides direction to use the L-isomer, rather than the D-isomer. Further, even if one wishes to argue that the compounds disclosed in cols 7-12 refer to a Markush group of the "D" isomer and the "L" isomer, there are at most only two possibilities, in which case both are obvious.

Next, it is argued (response, 4/21/03) that Cherksey does not disclose or suggest pure compounds, but instead discloses compositions that contain a mixture of D- and L-compounds. However, no passage where this might be disclosed has been indicated, and none is evident. Having begun with the premise that the Cherksey discloses only mixtures of D- and L- compounds, it is argued that the examiner has not explained how a peptide chemist of ordinary skill would "be motivated to modify the teachings of Cherksey '947 so that the required compounds are produced rather than a mixture of stereoisomers". The implied premise of this statement is that Cherksey discloses only how to make mixtures of D- and L- compounds, rather than optically pure compounds. However, this premise is inconsistent with the teachings of Cherksey, and inconsistent also with the statements in the declaration (filed 1/23/03). First, Cherksey does not disclose racemic mixtures, second, and in the declaration (filed 1/23/03) it is stated that no coupling between

arginine and spermidine occurs to begin with, so racemization in the final product cannot occur if, as asserted, the final product is never formed.

Next, it is argued (response, 4/21/03) that "the examiner has admitted that Cherkey does not teach substantially pure compounds". However, there has been no such admission by the examiner. Rather, the following statement was made by the examiner in the previous Office action:

"Cherksey does not employ the term 'substantially pure' to describe the compounds". This is different from saying that the reference fails to disclose compounds which are in fact substantially pure. The first point to bear in mind is that the epitome of 'substantially pure' is 100% purity. That is, the term "substantially pure" does not preclude the state or quality of being entirely pure. When a structure of a compound is provided in a reference, that structure represents a state of 100% purity. This is true whether the structure is in a reference book such as the Merck Index, or a textbook, or a patent. The organic chemist of ordinary skill is aware, however, that as a practical matter, trace impurities will almost always be present when one synthesizes a compound, or obtains it from a commercial source. For example, as any chemical reference book will disclose, the formula of benzene is C_6H_6. This formula represents a 100% pure compound. But if one synthesizes benzene, or purchases it from a commercial source, trace impurities will invariably be present. The impurities may be at the level of 1 ppm, or they may be at the

level of 1 part per billion. For example, the Aldrich Catalog (1993 edition) lists "99.9+%" benzene as the highest grade available. The "evaporation residue" is recited to be below 0.0005%, and the water level is recited to be below 0.05%. Thus, while C_6H_6 represents the formula of 100% pure benzene, the chemist of ordinary skill is aware that obtaining benzene in which impurities (organic or inorganic) are below the level of 1 ppm is going to be impractical. Thus, while the structure of a given compound represents the ideal of 100% purity, the chemist of ordinary skill is aware that as a practical matter, the best that one can achieve in reality is a compound that is merely "substantially pure". Moving on to the teachings of Cherksey, each and every one of the structures given in columns 7-12 of Cherksey represents a disclosure of a 100% pure compound. But as with any other compound for which a structure is given, elimination of all impurities beyond the 1 ppb level is not going to be practical. Thus, a chemist considering the structures present in cols 7-12 of Cherksey would recognize that in order to obtain the actual compounds (and not merely the structure on paper), the reality of trace impurities being present is inevitable. Thus, a chemist considering the structures disclosed in Cherksey, as with any other reference, would recognize that in endeavoring to obtain a physical sample of a compound, impurities will generally be present at a level of at least one part per trillion, and that as a consequence, such a compound can justifiably characterized as "substantially pure".

Next, it is argued that the examiner has not explained how a peptide chemist of ordinary skill would "be motivated to modify the teachings of Cherksey to provide substantially pure compounds as claimed. Cherksey does not disclose a method of making pure compounds as claimed". In the passage at col 18, line 54+ a procedure is disclosed for synthesis of compound "B" (col 8, third structure from last). In this procedure, L-arginine ethyl ester is dissolved in 1 N NaOH, and an equimolar quantity of spermidine is added dropwise. One can infer that Cherksey intends for nucleophilic displacement of ethanol to occur, thereby creating an amide bond. Various arguments have been offered (response filed 4/21/03) as to why this particular procedure is far from optimal. The examiner fully concurs with the assessment that this procedure is not optimal. However, there remain two other issues. First, the reaction procedure disclosed at col 18, line 54+ is not the only one disclosed. For example, at col 19, line 38+ a procedure is disclosed for synthesizing compounds BB and BB', both of which are encompassed by the instant claims. There has been no assertion that the disclosed procedure (col 19, line 38+) will fail to produce the intended compounds. The argument could stop here and be sufficient, at least for all of the claims that encompass compounds BB and BB'. But in addition, the claims are drawn to compounds *per se*, and not to methods of making compounds. The convention among peptide chemists is for the "L" isomer to be assumed when the structure of a compound is given, absent indication to the contrary. Thus, the peptide chemist of ordinary skill would

assume that the compounds disclosed in cols 7-12 are of the "L" configuration. In addition, the procedure at col 18, line 54 calls for the use of L-arginine, not D-arginine. Furthermore, even if it is true that there is ambiguity as to the stereochemistry of the compounds at cols 7-12, there are only two possibilities: "D" and "L". Given that there are only two such possibilities, neither could be properly described as unobvious.

The fundamental argument in the response (filed 4/21/03) is that the procedure at col 18, line 54 is non-enabling. However, there is no assertion provided that the procedure at col 19, line 38+ is non-enabling, and so at a minimum, the rejection is valid for compounds in which applicants' substituent variable "Q" represents amino. More importantly, even if it is true that the disclosed procedure is non-enabling for compounds in which "Q" represents amidino, the instant claims are drawn to compounds, not to a method of making compounds, and so the primary issue is whether Cherksey provides a disclosure of the claimed compounds, rather than a method of preparing the claimed compounds. The requisite stereochemistry is implied by the disclosed structures, and affirmatively stated for at least one compound (col 18, line 54+). Further, as stated (response filed 4/21/03, page 15):

> "Whether one having ordinary skill in the art would have had any difficulty making the claimed compounds is not relevant to patentability under 35 USC §103".

Even if it is true that one of the disclosed synthesis methods is inadequate, the claimed compounds *per se* are nevertheless disclosed.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of Bodansky (*Int J Pept Prot Res* **25**, 449-474, 1985).

The teachings of Cherksey were indicated previously. Bodansky is cited as showing the state of the art of peptide synthesis (at least in 1985).

In the response filed 4/21/03, it is argued that the examiner has only speculated as to what the ordinarily skilled peptide chemist might do if he "had some way of knowing it would be desirable to obtained applicants' claimed... compounds". However, Cherksey discloses the claimed compounds at cols 7-12. It is further disclosed that the compounds are useful for regulating cation transport. Thus, a scientist endeavoring to regulate cation transport would have been motivated to use the compounds disclosed in Cherksey for that purpose.

Next it is argued (response filed 4/21/03) that the compounds disclosed in Cherksey are not useful. However, no evidence has been provided that the compounds disclosed in Cherksey are not useful. Instead, evidence has been provided that if one combines arginine ethyl ester with spermidine in alkaline aqueous solution, the resulting mixture is cytotoxic, and therefore might not be useful. However, the examiner has never argued that a mixture of arginine ethyl ester and spermidine is (or is not) "useful".

Next it is argued (response filed 4/21/03) that (a) the prior art does not teach the desirability of the claimed compounds, (b) the prior art does not teach that the procedure at col 18, line 54+ of Cherksey provides unsatisfactory results. With respect to the first

point, Cherksey discloses that the compounds (cols 7-12) are useful for regulating cation transport. Thus, a scientist endeavoring to regulate cation transport would find the disclosed compounds to be "desirable". With respect to the second point, it is probably true that no reference of record discloses that the procedure at col 18, line 54+ of Cherksey will provide unsatisfactory results. At the same time, however, a chemist of ordinary skill, considering the teachings of Bodanszky, would have recognized the need for adequate protection of the amino groups. The same chemist of ordinary skill would have recognized that activation of the carboxyl group would have been necessary. As stated at page 450, col 1 of Bodanszky:

> "Carboxylic acids and amines do not yield amides spontaneously. Hence, formation of the peptide bond requires activation of one of the participating components... the carboxyl component has to be converted to a reactive form".

Thus, a chemist in possession of the Bodanszky reference would have been motivated to use one of the various methods of activating carboxylic acids such as a mixed anhydride or a nitrophenyl ester, or a carbodiimide.

Next, it is argued that Cherksey could have used the teachings of Bodanszky, but chose not to. It is further speculated that Cherksey was aware of the teachings of Bodanszky but disregarded his teachings because he found them to be unobvious. However, there is no evidence that Cherksey had considered the disclosure of this reference. One can only speculate as to the level of skill of Cherksey in the field of organic chemistry, and the

reasons for the choices he made. The decision by Cherskey to couple spermidine with arginine by the procedure disclosed at col 18, line 54+ does not constitute evidence that Cherskey is an organic chemist of ordinary skill.

Next, it is argued that there is no motivation to select the L-isomer. However, the "L" stereochemistry is implied in the structures given in cols 7-12. In addition, the L-isomer of arginine is suggested as a starting material, thereby signaling intent to produce the L-isomer. At worst, the reference can be interpreted to disclose a Markush Group of "D" and "L" isomers, in which case both are obvious. Next, it is argued that the compounds disclosed at cols 7-12 are lethal, and so a chemist would have decided not to use the compounds. However, no evidence has been presented which shows that the compounds disclosed at cols 7-12 are lethal, although it may be true that a mixture of arginine ethyl ester and spermidine is cytotoxic.

Thus, Cherksey discloses the claimed compounds, and taken together with the disclosure of Bodanszky, methods of synthesizing the claimed compounds would have been obvious to the organic chemist of ordinary skill.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of the Aldrich Catalog, 1992-1993 edition.

The teachings of Cherksey were indicated previously. Cherksey does not explicitly

state that the structures at cols 7-12 are limited to the L-isomer. As indicated previously, the Aldrich Catalog (1992-1993 edition) lists both stereoisomers of arginine. The price difference is dramatic; the "D" isomer is more than 100 times more expensive than the "L" isomer. The peptide chemist of ordinary skill would have been motivated to synthesize the compounds disclosed in cols 8-9 (or cols 10-12) using the "L" isomer because of the lower cost.

The response to the foregoing focuses on the passage at col 18, line 54+, wherein a reaction between arginine ethyl ester and spermidine is disclosed. The essence of the argument is that if the disclosure of Cherksey were limited to the passage at col 18, line 54+, the "L" isomer in the final product would not have been obvious because of racemization, and because the passage in question makes reference to arginine ethyl ester, rather than arginine *per se*. As conceded by the examiner above, the reaction described at col 18, line 54+ is not an optimal means of obtaining the claimed compound. However, the instant claims are drawn to compounds (and compositions), and not to a method of synthesizing compounds. Irrespective of what coupling agent is used, and which amine protecting group is used, the peptide chemist of ordinary skill would have recognized, upon viewing structure "R" (col 9, Cherksey) that this compound would be best synthesized beginning with arginine, or a derivative of arginine. Accordingly, arginine *per se* would have to be purchased, or else a derivative of arginine. Whether arginine itself is purchased, or a

derivative of arginine, the cost of the D-isomer will be considerably greater than the cost of the L-isomer. The peptide chemist of ordinary skill is not compelled by Cherksey or by the instant claims to pursue one synthetic path over another. The issue of what may be disclosed at col 18, line 54+ is not controlling. What matters is that (a) the claimed compounds are disclosed (even if there may be ambiguity as to stereochemistry), and (b) the peptide chemist of ordinary skill would recognize that many of the claimed compounds would be synthesized beginning with arginine as a starting material. Given that both of these are true, the only remaining issue is that of the choice between the "L" isomer, and the "D" isomer. The Aldrich Catalog provides a motivation to select the "L" isomer.

The rejection is maintained.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of Eldefrawi (*Proc. Natl. Acad. Sci. U. S. A.* 85(13), 4910-13, 1988).

The teachings of Cherksey were indicated previously. Cherksey also teaches (col 13, line 49+) that the procedures disclosed in Eldefrawi may be used. Eldefrawi discloses (p. 4912, col 1) that compound 9 was reacted with compound 6 to produce compound 2. Eldefrawi des not disclose any of the claimed compounds.

In response to the foregoing (response, 4/21/03), it is argued that the "target" compounds

are not disclosed in Cherksey. However, they are disclosed in cols 7-12. The response disregards the disclosure of the target compounds in Cherksey, and instead focuses on the compounds which might be produced by the procedure disclosed at col 18, line 54+. However, this ground of rejection is from the perspective of a chemist who has made the decision to synthesize one of the compounds disclosed in cols 7-12 in order to regulate cation transport. As indicated above, Cherksey teaches (col 13, line 49+) that the procedures disclosed in Eldefrawi may be used to synthesize the compounds disclosed in cols 7-12. Eldefrawi discloses reaction of a polyamine with an active ester of a protected amino acid, wherein all but one of the amino groups of the polyamine is protected. The synthetic chemist of ordinary skill would have taken from this the conclusion that in reacting a polyamine with an acylating agent (e.g., lysine or arginine + activating agent), that all of the amino groups should be protected except for the one which is intended to form an amide bond. Cherksey provides a specific suggestion to employ the procedures disclosed in Eldefrawi. Accordingly, there is no question as to the motivation to combine the synthetic methods of Eldefrawi with the disclosure of the target compounds given in Cherksey. Together, these references provide a fully enabling disclosure not only of target compounds themselves, but a method of making them as well.

Thus, the claims are rendered obvious.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of Hashimoto (*Tetrahedron Lett.* **28**(30), 3511-14, 1987).

The teachings of Cherksey were indicated previously. Cherksey also teaches (col 13, line 50+) that the procedures disclosed in Hashimoto may be used. Hashimoto discloses that compound 5 was reacted with spermine to produce compound 4. Hashimoto does not disclose any of the claimed compounds.

In response to the foregoing, it is argued (response, 4/21/03) that the examiner has not explained how an organic chemist of ordinary skill would have used the teachings of Hashimoto to modify the teachings of Cherksey. This ground of rejection is from the perspective of a chemist who has decided to synthesize one of the compounds disclosed in cols 7-12, and has decided to use the suggestion (col 13, line 50+, Cherksey) to use the procedures disclosed in Hashimoto, rather than the procedure at col 18, line 54+ of Cherksey.

Compound 5 of Hashimoto is an acylating agent, and may be represented as "RCO-X", wherein "X" is a leaving group. Hashimoto discloses the following reaction:

$$RCO\text{-}X + \text{spermine} \rightarrow RCO\text{-}NH(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$$

If a chemist were presented with a structure such as compound "S" of Cherksey (col 9) or compound "NN" (col 11), he would have taken from Hashimoto the suggestion that reaction of an acylating agent with a symmetrical polyamine would afford the target compound.

The acylating agent would be lysine or arginine in which the amino groups are protected, and the activated ester is *para*-nitrophenol.

The rejection is maintained.

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Claims 1, 2, 5, 6, 8, 19-24 are rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (USP 5,242,947) in view of Bodanszky (*Int J Pept Prot Res* **25**, 449-474, 1985) further in view of the Aldrich Catalog, 1992-1993 edition.

The teachings of Cherksey were indicated previously. Cherksey also discloses (col 13, line 35+ that spermidine is commercially available. Cherksey does not explicitly state that the structures at cols 7-12 are limited to the L-isomer.

Bodanszky discusses the state of the art of peptide synthesis (as of 1985). Bodanszky discloses that (a) peptides are synthesized by coupling amino acids, (b) nucleophilic groups on the reactants must be protected, and (c) carboxyl group activation is required for amide bond formation to occur. Bodanszky does not teach any of the claimed compounds.

As indicated previously, the Aldrich Catalog (1992-1993 edition) discloses that D-arginine is more than 100 times more expensive than the "L" isomer. The peptide chemist of ordinary skill would have been motivated to synthesize the compounds disclosed in cols 8-9 (or cols 10-12) using the "L" isomer because of the lower cost.

This ground of rejection is imposed from the perspective of the peptide chemist of ordinary

skill who has made the decision to synthesize one of the structures disclosed in Cherksey, such as compound "R" (col 9). Upon considering the disclosure of Bodanszky, the chemist would recognize that this compound would be best synthesized by coupling a derivative of arginine with spermidine. As disclosed in Cherksey, sperimidine is commercially available. As stated at page 450, col 1 of Bodanszky, activation of the carboxyl component is necessary when coupling an amine with a carboxylic acid to form an amide. In addition, Bodanszky discloses that protection of nucleophilic groups is necessary in order to avoid formation of undesired products. Thus, the peptide chemist of ordinary skill would recognize that the target compound can be synthesized by reacting N^{α}-protected arginine with spermidine in the presence of a coupling agent, and wherein all but one of the amino groups of spermidine are protected. The peptide chemist would further choose to use L-arginine, rather than D-arginine because of the lower cost of the L-isomer.

In accordance with the foregoing, Cherksey provides the synthetic "target", Bodanszky provides direction as to how to achieve the synthesis, and the Aldrich catalog provides motivation to select the L-isomer. Thus, the claims are rendered obvious.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 5/27/03

Christopher S. F. Low
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